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A study of the cardiovascular effects of the direct acting anti-hepatitis C virus drugs by cardiac magnetic resonance imaging

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ABSTRACT

Objectives: Chronic Hepatitis C Virus infection is highly prevalent in Egypt. The introduction of the new direct acting antivirals has revolutionized the treatment of HCV patients. Our study aimed to evaluate the effects of these drugs on the cardiovascular system, using cardiac Magnetic Resonance Imaging (CMR). *Methods:* Twenty-one treatment naïve adult patients with no prior history of cardiovascular disease and free from cardiovascular risk factors were included in the study. Each subject had a negative treadmill stress ECG test before starting treatment. *Results:* Treatment with direct-acting antivirals (DAAs) had no effect on LV dimensions, biventricular volumes, and functions. There was also no difference noted regarding resting segmental wall motion abnormalities (RSWMA) by Trans-Thoracic Echocardiography (TTE) and CMR and late gadolinium enhancement (LGE) by CMR. *Conclusion:* The DAAs used in the national protocol for HCV treatment in Egyptian patients have potentially good cardiac safety profile. There were no changes in biventricular functions by TTE or CMR and no myocardial fibrosis detected by CMR in the studied patients. These highly effective drugs potentially had no cardiotoxic effects in Egyptian patients.

Keywords: Hepatitis C virus, direct acting antiviral agents, Cardiac Magnetic Resonance Imaging.

1. INTRODUCTION

Chronic infection by hepatitis C virus (HCV) is prevalent worldwide; with global estimates as high as 1% of world population (Polaris Observatory HCV Collaborators, 2017). Historically, Egypt possessed the highest HCV prevalence, mainly because of using unsafe parenteral injections in the mass treatment of schistosomiasis in the 20th century (Frank et al., 2000). In the recent years, Egypt has implemented a successful HCV screening and

treatment program, which led to nationwide screening of 49.6 million people between October 2018 and April 2019. 2.2 million HCV cases were identified from this mass screening, and they were referred for further evaluation (Waked et al., 2020). HCV treatment has witnessed major improvement owing to the introduction of the direct-acting antiviral (DAA) agents. However, there were some questions raised about their cardiac safety profile. Some case reports and studies reported possible cardiac side effects from DAAs, such as cardiomyopathies and conduction disturbance (Ahmad et al., 2015; Petta et al., 2016; Sherman et al., 2013).

Cardiac Magnetic Resonance Imaging (CMR) is considered the gold standard modality for objective calculation of ventricular volumes and systolic functions, without worrying about the echocardiographic windows or the inter-observer variability. The addition of gadolinium enhancement to CMR studies enables the detection of myocardial fibrosis and scarring which can be used to diagnose any cardiac affection before its detection clinically and even before causing evident impairment of ventricular functions. Additionally, the pattern of late gadolinium enhancement (LGE) helps in differentiating between ischemic and non-ischemic cardiomyopathies (Hundley et al., 2010).

We aimed to evaluate the cardiovascular (CV) effects and safety of the DAAs in Egyptian HCV patients using CMR, to detect and quantify changes in biventricular volumes, systolic functions, resting segmental wall motion abnormalities (RSWMA), myocardial scarring and fibrosis after treatment with DAAs.

2. MATERIALS AND METHODS

This is a prospective observational study conducted on 24 treatment-naïve adult HCV patients ($\geq$ 18 years) with a positive polymerase chain reaction (PCR) test. Patients were recruited from the HCV specialized outpatient clinic in the period between February 2019 and November 2019. They voluntarily agreed to participate in this study and provided written informed consent. The exclusion criteria were the following: previous history of cardiac diseases; having conventional CV risk factors (smoking, diabetes mellitus, hypertension, dyslipidemia, family history of premature coronary artery disease CAD); decompensated liver cirrhosis (Child-Pugh score C) (Pugh et al., 1973); hepatic or extrahepatic malignancy; pregnant women; platelets count < 50000/mm^3 ; having other causes of chronic liver diseases, intravenous drug abuse; heavy alcohol consumption; patients with end-stage renal disease; and having contraindications to CMR (Hundley et al., 2010). All participants were treated per the national chronic HCV treatment protocol: sofosbuvir 400 mg daily with daclatasvir 60 mg daily for 12 weeks (Doss et al., 2016; El Raziky et al., 2016).

Clinical history and baseline investigations

Full clinical assessment was done to all participants, including full clinical history to identify those with any of the forementioned exclusion criteria. Height and weight (in centimeters (cm) and kilograms (kg) respectively) were taken to calculate body surface area (BSA) in m^2 using the Mosteller formula: "BSA = square root of (height in cm x weight in kg) / 3600" (Mosteller, 1987). Blood samples were taken from all subjects to measure liver enzymes, total bilirubin, serum albumin, full blood count, international normalized ratio, kidney function tests and electrolytes, glycated hemoglobin, fasting blood sugar, HCV PCR, HCV antibodies, and surface antigen of hepatitis B. Alfa fetoprotein was measured to exclude hepatocellular carcinoma and beta-HCG in premenopausal females to exclude pregnancy.

Cardiac investigations

Resting 12 lead surfaces Electrocardiography (ECG) was done to all subjects at baseline to assess heart rate, rhythm, and the presence of any ischemic changes. Additionally, treadmill stress ECG testing was completed by all subjects before initiating the treatment to exclude the presence of significant CAD. The following tests were performed on all participants before treatment initiation and 1-2 weeks after completing treatment:

Resting Trans-thoracic Echocardiography (TTE): standard ECG-gated TTE using a GE S7 machine using an M4S matrix sector array probe having a frequency range from 1.7 to 342 mega Hertz (GE, Vingmed, Horten, Norway). A full TTE standard study was done following guideline-recommended protocols (Mitchell et al., 2019) to obtain:

LV internal dimensions: LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD) measured by the two-dimensional mode from the parasternal long-axis view at a level just below the mitral valve (MV) leaflets tips; and LV ejection fraction (LVEF) calculated from the apical views by the biplane disk summation method (Mitchell et al., 2019).

Assessing LV diastolic function: measuring trans-mitral E/A ratio, deceleration time (DT), tissue Doppler on lateral mitral annulus to measure the first negative wave velocity (E'), and E/E' ratio (Mitchell et al., 2019).

Right ventricular (RV) function assessment: measuring the RV systolic pressure (RVSP), estimating mean pulmonary artery pressure, and using M-mode to measure the tricuspid annular plane systolic excursion (TAPSE) (Mitchell et al., 2019). Cardiac MRI with and without contrast (Gadolinium) to calculate ventricular volumes, systolic functions and detect fibrosis (by LGE), was performed on a 1.5 Tesla scanner (Philips, Ingenia 1.5 T SE). Each CMR study comprised the following:

Scout imaging: trans-axial, coronal, and sagittal.

Steady-state free precession (SSFP) cine images (short axis, 4 chamber long axis, vertical long axis, LV outflow tract long axis).

LGE imaging: using 2D segmented inversion recovery SSFP, Phase-Sensitive Inversion Recovery (PSIR) pulse sequences (Hundley et al., 2010).

Of the 24 subjects, one was excluded because of having a positive treadmill stress test before initiating the treatment, one was excluded due to treatment discontinuation, and one withdrew from the study.

3. RESULTS

Baseline Characteristics and clinical data

Demographic data, clinical characteristics, and baseline laboratory investigations are shown in Table 1.

Table 1 Demographics, clinical characteristics, and baseline laboratory investigations

Clinical Characteristics	
Age (years),	43.62 ± 14.16
Male gender, number (%)	13 (61.9%)
Weight (Kg)	78.29 ± 15.25
Height (cm)	174.95 ± 7.35
Body Surface Area (m^2)	1.95 ± 0.21
Alanine transaminase (IU/L)	43.33 ± 27.87
Aspartate transaminase (IU/L)	42.71 ± 28.06
Alpha feto-protein (ng/ml)	5.69 ± 11.21
Serum Albumin (g/dL)	4.29 ± 0.42
Total Bilirubin (mg/dL)	0.8 ± 0.36
Indirect Bilirubin (mg/dL)	0.53 ± 0.26
Total leucocytic count (x 10^9 / L)	6.23 ± 1.7
Hemoglobin (g/dL)	12.46 ± 2.14
Serum Creatinine (mg/dL)	0.87 ± 0.14
International Normalized Ratio	1.04 ± 0.09
Platelets count (x 10^9 / L)	256.52 ± 70.6

Continuous variables are expressed as mean and standard deviation whereas categorical variables are expressed as number (percentage). Effects of treatment on cardiac function are shown in tables 2 and 3. Treatment with DAAs had no effect on LV dimensions (by TTE), biventricular volumes (by CMR), biventricular systolic (by TTE and CMR) and diastolic (by TTE) functions. We also found no difference in the study population before and after treatment with DAAs regarding resting segmental wall motion abnormalities (RSWMA) by TTE & CMR and Late Gadolinium Enhancement (LGE) by CMR (figure 1& 2).

Table 2 CMR data in subjects before and after treatment with DAAs.

CMR variables	Baseline	After treatment	P value
LV EDV (ml)	143.7 ± 25.23	145.38 ± 24.87	0.138
LV EDVI (ml/m^2)	73.53 ± 7.87	74.76 ± 7.84	0.122
LV ESV (ml)	54.8 ± 14.62	55.93 ± 14.48	0.225
LV ESVI (ml/m^2)	27.82 ± 4.67	28.42 ± 4.48	0.217
SV (ml)	88.91 ± 13.46	89.36 ± 12.77	0.552
SVI (ml/m^2)	45.73 ± 5.84	45.93 ± 5.55	0.63
LV EF (%)	62.43% ± 4.13%	61.95% ± 3.65%	0.219

RV EDV (ml)	143.24 ± 21.94	145.19 ± 20.75	0.140
RV EDVI (ml/m^2)	73.56 ± 9.8	74.51 ± 9	0.175
RV ESV (ml)	55.77 ± 10.45	57.38 ± 10.07	0.126
RV ESVI (ml/m^2)	28.69 ± 5.35	29.52 ± 5.13	0.129
RV EF (%)	60.24% ± 4.28%	59.71% ± 3.89%	0.341
RSWMA, number (%)	0 (0%)	0 (0%)	
LGE, number (%)	0 (0%)	0 (0%)	

LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEDVI: indexed left ventricular end-diastolic volume, LVESVI: indexed left ventricular end-systolic volume, LVEF: left ventricular ejection fraction, RVEDV: right ventricular end-diastolic volume, RVESV: right ventricular end-systolic volume, RVEDVI: indexed right ventricular end-diastolic volume, RVESVI: indexed right ventricular end-systolic volume, RVEF: right ventricular ejection fraction, SV: stroke volume, SVI: indexed stroke volume, RSWMA: resting segmental wall motion abnormalities, LGE: late gadolinium enhancement.

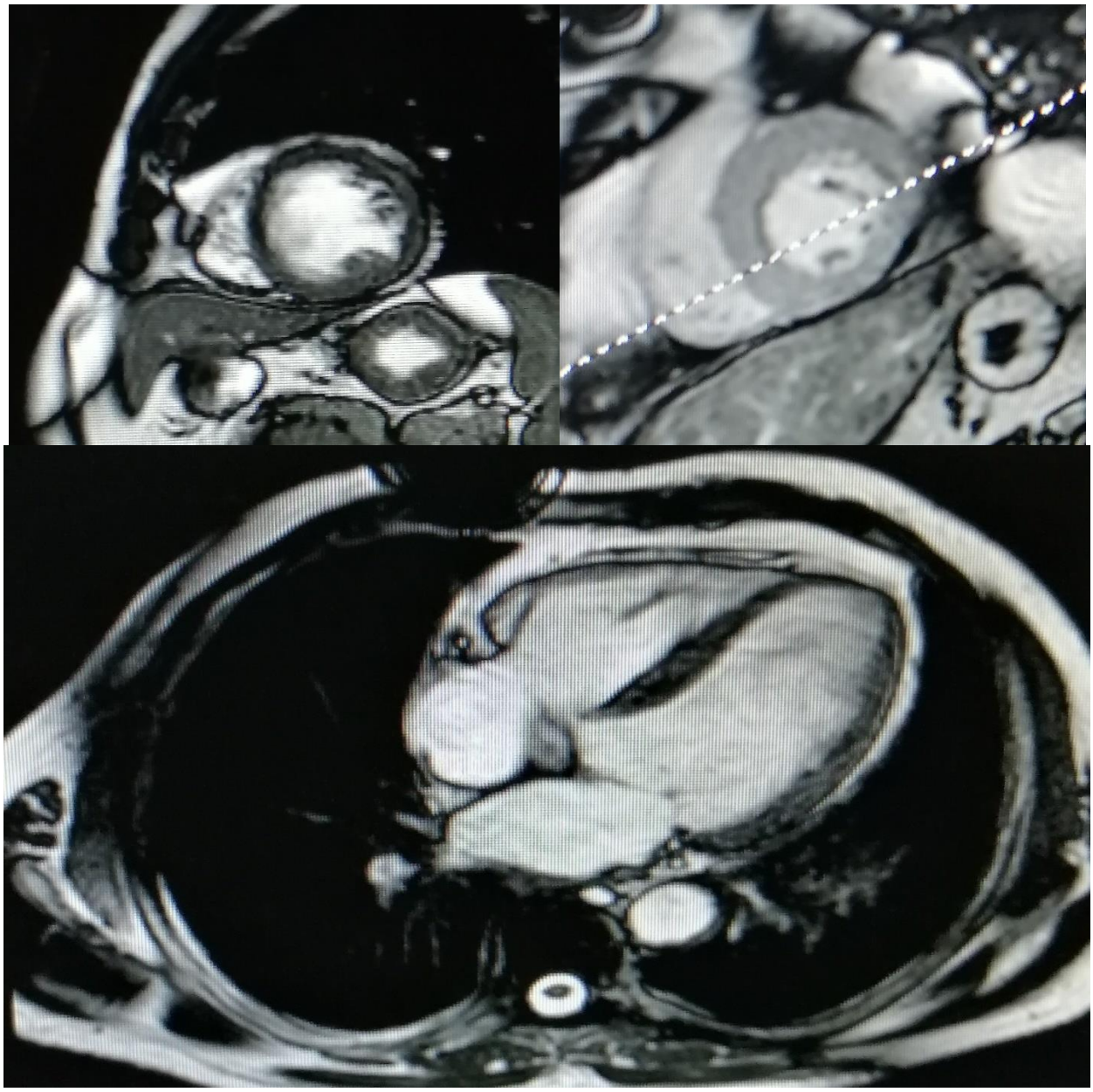

Figure 1 CMR study in subject (17) after DAA. Upper left: Short axis cine image. Upper right: PSIR sequence in short axis with no LGE. Bottom: Apical 4 chamber cine image.

Table 3 Trans-Thoracic echocardiography (TTE) data in subjects before and after DAAs.

TTE variables	Baseline	After treatment	p value
LVEF (%)	64.29% ± 3.95%	64.24% ± 3.52%	0.910
FS (%)	34.71 ± 2.92	34.67 ± 2.74	0.858
LVEDD (mm)	47.1 ± 5.8	47.43 ± 5.36	0.184
LVESD (mm)	30.43 ± 4.19	30.81 ± 3.59	0.214
IVSTD (mm)	8.71 ± 1.45	8.9 ± 1.25	0.103
PWTD (mm)	8.67 ± 1.59	8.86 ± 1.46	0.258
LAD (mm)	36.05 ± 3.53	36.48 ± 3.49	0.131
RVSP (mmHg)	26.52 ± 2.71	26.71 ± 3.04	0.662
RSWMA, number (%)	0 (0%)	0 (0%)	
LV DD, number (%)	9 (42.9%)	11 (52.4%)	0.54

LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, IVSTD: inter-ventricular septum thickness in diastole, PWTD: posterior wall thickness in diastole, LVEF: left ventricular ejection fraction, FS: left ventricular fractional shortening, LAD: left atrial diameter, RVSP: right ventricular systolic pressure, RSWMA: resting segmental wall motion abnormalities, LVDD: LV Diastolic Dysfunction.

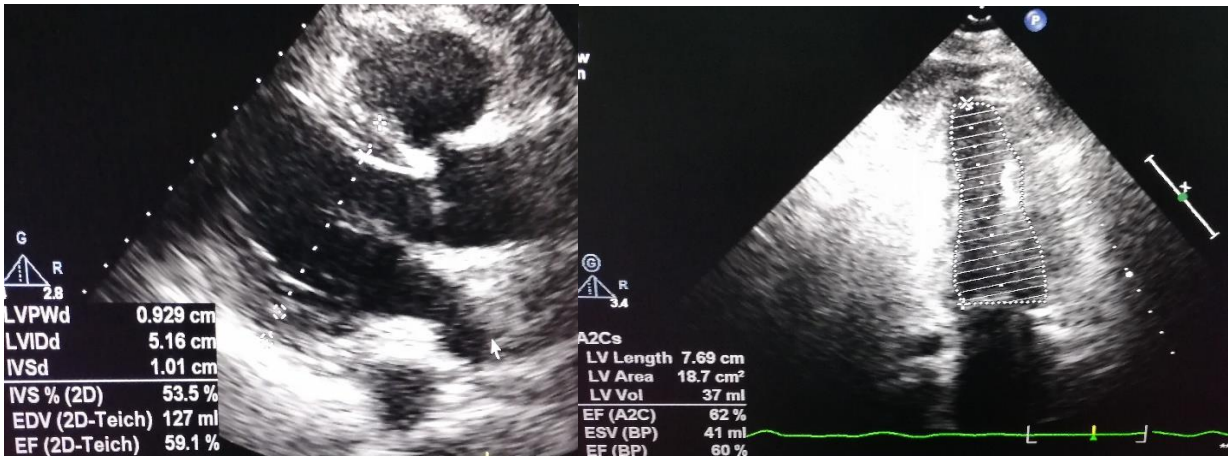

Figure 2 TTE study in subject (10) after DAAs. Left: parasternal long axis view to measure LV end diastolic diameter. Right: Apical 2 chamber view to calculate LVEF by biplane disc summation.

4. DISCUSSION

HCV infection is a worldwide problem and a leading cause of cirrhosis and liver cancer, thus representing a huge social and economic burden. Egypt is of the countries with the highest prevalence of HCV infection (Waked et al., 2020). The introduction of the oral DAAs has led to a major shift in the treatment guidelines of chronic HCV and consequently the prognosis of HCV patients. However, their cardiac safety remains debatable (Ahmad et al., 2015; El Raziky et al., 2016). This study aimed to evaluate the CV effects and safety of the new DAAs in Egyptian patients with HCV infection using CMR. All subjects were treatment-naïve adults having no previous history of CV disease and no conventional CV risk factors. Additionally, to eliminate any possible confounders, all the subjects underwent treadmill stress ECG testing prior to treatment initiation, to exclude those with undiagnosed CAD.

Our results showed that DAAs used in the national Egyptian HCV treatment protocol have no effect on cardiac functions; with all the TTE and CMR measurements remaining in the normal range, with no fibrosis detected by LGE in CMR and no resting segmental wall motion abnormalities (RSWMA) evident either by CMR or TTE. We concluded also that DAAs have no effect on biventricular dimensions, volumes and functions assessed by guideline-recommended measurements by CMR and TTE. This is one of the first studies to assess LV and RV functions by CMR in HCV patients receiving DAAs after the exclusion of possible confounders.

Our findings agree with Biomy et al., (2017) who concluded that DAAs do not significantly affect the CV system. After studying 170 HCV patients receiving different DAAs, they reported that none of them developed any major cardiac events, or any RSWMA or significant changes in systolic or diastolic function parameters by TTE. The new DAAs were also found to have a good cardiac

safety profile in the study by Ibrahim et al., (2020). They performed resting ECG and TTE to 100 HCV patients before and 12 weeks after treatment with DAAs, reporting no changes in biventricular dimensions, LV ejection fraction (EF), LV global longitudinal strain (GLS), all RV function parameters except for RV GLS, which worsened in the non-cirrhotic group only, although remaining in the normal reference range (p=0.024). LV diastolic function parameters also showed no significant changes before and after DAAs, apart from minor changes in the lateral E' mitral annular velocity and in the indexed left atrial volume (LAVI) in the cirrhotic group, with both also remaining within the normal reference range.

On the contrary, Mazzitelli et al., (2018) evaluated the cardiac functions by TTE before and after DAA treatment in 82 HCV patients. Their results showed no variations in LVEF, but they noted unexpected worsening of LV function when measured through GLS. However, they reported that the response was different in their two groups. The group of patients who received DAAs for three months (group A) showed initial improvement in GLS after 1 month, then at the end of the study there was significant worsening in GLS in this group (p= 0.031). Meanwhile, group B subjects, who received DAAs for six months, did not show the same biphasic trend noted in group A. Group B showed a steady tendency towards a statistically significant worsening from (p= 0.097) (Mazzitelli et al., 2018). It is worth mentioning that the GLS values in both groups at the end of the study follow up remained within the normal range (Perk et al., 2018). They stated that they had no explanation to their findings and that it could have been due to the small sample size, or due to the presence of possible confounders (Mazzitelli et al., 2018).

Our findings also agree with the findings reported by Novo et al., (2016). They reported no change in LV EF, dimensions, volumes, GLS, and all the other different TTE parameters, except slight improvement of two parameters in cirrhotic patients after treatment with DAAs: TAPSE ($P < 0.01$) and lateral E' velocity ($P = 0.001$). On the other hand, El-Adawy et al., (2018) examined different DAA treatment regimens and their cardiac safety using CMR and creatine kinase MB fraction (CK-MB) in 390 patients. CMR was done before, during, and 6 months after treatment. The groups receiving sofosbuvir and daclatasvir +/- ribavirin showed significant rise in their CK-MB levels, and changes in CMR (namely: increased tissue edema, early gadolinium enhancement and LGE) in comparison with other groups. However, these CMR and laboratory changes were fully reversible without leaving any permanent damage to the CV system after stopping the DAAs. However, these results could be due to the presence of other confounders, such as the demographic data and CV risk factors of the subjects in the different treatment groups, of which there was no mention or statistical analysis published. They also stated that, despite these findings and differences in CMR data between the different groups, DAAs could be safely administered, as these changes were fully reversible with no permanent damage to the heart (El-Adway et al., 2018).

Additionally, there are other studies on DAAs, focusing mainly on the conduction system of the heart. El Missiri et al., (2020) reported that there were no symptomatic bradycardias, tachycardias, or syncope detected using 24-hour ECG monitoring in 50 HCV patients with no prior cardiac history, receiving sofosbuvir and daclatasvir. Ibrahim et al., (2020) also reported no change in the corrected QT interval in HCV patients before and after DAAs.

Study limitations

This was a single-center study, with the participants being from one geographical region. Futurelarger studies are required to confirm our findings. Follow-up was performed only once 1-2 weeks after the end of treatment. Studies with longer follow-up periods are needed to study the long-term cardiac safety of the new DAAs. Patients with underlying CV conditions and those with conventional CV risk factors were excluded. Studies focusing on these groups are required.

5. CONCLUSION

The DAAs used in the national HCV treatment protocol in Egyptian patients have potentially good cardiac safety profile. There were no changes in biventricular functions by TTE or CMR and no myocardial fibrosis detected by CMR in the studied patients. These drugs, in addition to being highly effective in viral eradication, potentially had no cardiotoxic effects in Egyptian patients.

Ethical approval

Approval of Faculty of Medicine Ain Shams University Research Ethics Committee (FMASU REC, FWA 000017585) was obtained for this study. The committee reference number is: FMASU M D 157/ 2018.

Informed consent

Written and oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AGS was a major contributor in data collection in addition to writing the manuscript, DK was the main contributor in the study design and in data analysis, YE revised the data set and participated in statistical analysis, ASI was the main contributor in analysis of the MRI studies, OAA supervised the patients' recruitment and data collection, TMKA revised the data set and participated in data analysis. All authors read and approved the final manuscript.

Abbreviation

BSA: body surface area.
CAD: coronary artery disease.
CK: creatine kinase.
CMR: cardiac magnetic resonance imaging.
CV: cardiovascular.
CVD: cardiovascular disease.
DAAs: direct-acting antivirals.
DT: deceleration time.
ECG: electrocardiogram.
EDV: end-diastolic volume.
EDVI: end-diastolic volume-indexed.
ESV: end-systolic volume.
ESVI: end-systolic volume-indexed.
FS: fractional shortening.
GLS: global longitudinal strain.
HCG: human chorionic gonadotropin.
HCV: Hepatitis C virus.
IVSTD: inter-ventricular septum thickness in diastole.
LAD: left atrial diameter.
LAVI: left atrial volume indexed.
LGE: late gadolinium enhancement.
LV: left ventricular.
LVDD: left ventricular diastolic dysfunction.
LVEDD: left ventricular end-diastolic diameter.
LVEF: left ventricular ejection fraction.
LVESD: left ventricular end-systolic diameter.
PCR: polymerase chain reaction.
PSIR: phase sensitive inversion recovery.
PWTD: posterior wall thickness in diastole.
RSWMA: resting segmental wall motion abnormalities.
RV: right ventricular.
RVEF: right ventricular ejection fraction.
RVSP: right ventricular systolic pressure.
SSFP: steady state free precession.
SV: stroke volume.

SVI: stroke volume- indexed.
TAPSE: tricuspid annular plane systolic excursion.
TTE: trans-thoracic echocardiography.

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